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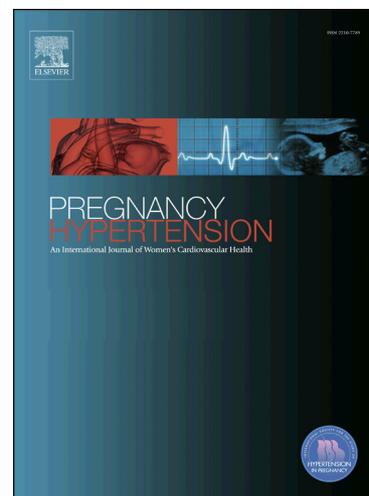
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Inherited predisposition to preeclampsia: analysis of the Aberdeen intergenerational cohort

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Abstract

Objective: To assess the magnitude of familial risk of preeclampsia and gestational hypertension in women born of a preeclamptic pregnancy and those born of pregnancy complicated by gestational hypertension while accounting for other risk factors.

Methods: An intergenerational dataset was extracted from the Aberdeen Maternity and Neonatal Databank (AMND) which records all pregnancy and delivery details occurring in Aberdeen, Scotland since 1950. The analysis included all nulliparous women whose mothers' records at their births are also recorded in the AMND. Multinomial logistic regression was used to assess the risk of having preeclampsia or gestational hypertension based on maternal history of preeclampsia or gestational hypertension.

Results: There were 17302 nulliparous women included, of whom 1057(6.1%) had preeclampsia while 4098(23.7%) had gestational hypertension. Furthermore, 424(2.5%) and 2940(17.0%) had maternal history of preeclampsia and gestational hypertension respectively. The

risk of preeclampsia was higher in women who were born of pregnancies complicated by preeclampsia (adjusted RRR 2.55 95% CI 1.87–3.47). This was higher than the risk observed in women whose mothers had gestational hypertension (adjusted RRR 1.44 95% CI 1.23–1.69). Conversely, the risk of gestational hypertension was similar in those who were born of preeclamptic pregnancies (adjusted RRR 1.37 95% CI 1.09–1.71) and those whose mothers had gestational hypertension (adjusted RRR 1.36 95% CI 1.24–1.49).

Conclusion: There was a dose response effect in the inheritance pattern of preeclampsia with the highest risk in women born of preeclamptic pregnancies. Gestational hypertension showed similar increased risk with maternal gestational hypertension and preeclampsia.

Key words: preeclampsia, intergenerational, gestational hypertension, risk factors

INTRODUCTION:

About 14% of all maternal deaths worldwide are attributable to hypertensive disorders of pregnancy [1]. Preeclampsia, the symptom complex of hypertension, proteinuria and oedema, is a multifactorial disorder of pregnancy which is associated with significant maternal and perinatal complications. It is now known that women who had preeclampsia as well as their offspring are at increased risk of chronic disease [2]. While the exact cause of preeclampsia is not known, the risk factors associated with its development include race, parity, age, body mass index (BMI), size of the baby and the placenta as well as pre-existing diabetes and cardiovascular disease [3]. Interestingly, factors such as smoking

[4] and unprotected sexual intercourse [5] have been associated with reduced risks. It is clear that there is a need for a better understanding of the pathogenic mechanism of preeclampsia.

The first definitive study into the epidemiology of preeclampsia is credited to Chesley in 1978 [6]. Since then, several epidemiological and genetic studies have confirmed a familial tendency to develop preeclampsia [7-11]. Two large population based studies conducted in Norway [12,13] and Sweden [14,15], have investigated the relative contributions of maternal and fetal genetic factors in the pathogenesis of preeclampsia. Lie suggests that maternal contributions are twice as strong as paternal ones, and may occur through the maternal genomic alleles as well as the intrauterine environment [16]. The mother also provides fetal mitochondria, but this mechanism is unlikely to be responsible for incurring genetic susceptibility to preeclampsia [13]. Despite the plethora of studies identifying genetic markers for the condition, multiple genetic risk factors are likely to contribute to the risk.

Although there is considerable accumulated evidence on the genetic susceptibility to preeclampsia, the magnitude of such effects in the presence of other risk or protective factors is largely under-researched. The aim of this study was to assess the magnitude of familial risk of preeclampsia in women born of preeclamptic pregnancy and pregnancies complicated by gestational hypertension compared to those born of normotensive pregnancy while controlling for other known predictive factors. We also assessed the risks of gestational hypertension in the same group of women.

METHODS:

Description of the cohort

The Aberdeen Maternity and Neonatal Databank (AMND) was established by Sir Dugald Baird in 1950 to store records of all pregnancy related events occurring in Aberdeen, Scotland [17]. This database is maintained to this day, and is perhaps the oldest database of its kind that has been in continuous use. It now holds information on more than 274,323 pregnancies and is being added to on a weekly basis. Since Aberdeen has a relatively stable population and is served by a single maternity unit, the opportunities for research presented by the AMND soon became obvious; but it was not until the early 1980s that the idea of establishing an intergenerational cohort materialised. Carr-Hill et al used this intergenerational cohort to study the effects of inheritance on birth weight [18]. Following on from this study, when only relatively small numbers of intergenerational pairs could be utilised (n=505) the cohort has grown considerably over time as women within families reproduced.

We used data from pregnancy records from 1950 to 2008. Within the Scientific Information Retrieval system (SIR) which was used to store the data, relatives were identified as mother-daughter pairs by matching the mother's surname and date of delivery to the daughter's maiden name and date of birth. NYSIIS and SOUNDSEX software were utilised for identifying names that were similar. However, only cases with exact matches on the date of birth/ delivery were accepted. The current analysis includes women whose mothers' pregnancy and delivery data were available in the database.

Variables used in the analysis

Preeclampsia, eclampsia and gestational hypertension are coded in the AMND according to the ISSHP definition as follows: Gestational hypertension is defined as a diastolic blood pressure of ≥ 110 mmHg on any one occasion or diastolic blood pressure of ≥ 90 mmHg on any two

or more occasions at least 4 hours apart; and preeclampsia as hypertension as above with proteinuria of ≥ 300 mg/24 hours or proteinuria found in 2 urine specimens collected at least 4 hours apart [19]. The small number of cases with eclampsia (with superadded convulsions) was included in the preeclampsia group.

Social class based on women's husband or partner's occupation, is coded in the AMND according to the British Registrar General's occupational social class classification of 1951 into 6 categories: I- professional, II- managerial, III- skilled non-manual, IV- skilled manual, V- semi-skilled, VI- unskilled. This classification was recoded into 2 categories for ease of analysis: professional/ non-manual (Classes I to III) and manual (Classes IV to VI)

BMI was calculated using the formula weight in kilograms divided by height in metres squared. The height and weight used were those measured and recorded by clinical staff at the first antenatal booking visit, as long as it was within 20 weeks of gestation. Gestational age is recorded according to the date of the last menstrual period as reported by women and then confirmed by ultrasound since 1986. As much of the data pre-dates routine use of ultrasound, gestational age is mostly calculated according to dates. Other variables extracted included self-reported smoking habits recorded during antenatal clerking as the number of cigarettes smoked per day and the age of the woman at first delivery.

STATISTICAL ANALYSIS

The women were categorised into three groups; those who were normotensive, those who had gestational hypertension and those who had preeclampsia (including those with eclampsia). Multinomial logistic regression analysis was used to determine the association between having maternal history of preeclampsia or gestational hypertension and the three grouping categories. The normotensive group was used as the reference category. The analysis was adjusted for age at first birth, BMI, smoking status and social class. The strength of association was reported using adjusted relative risk ratios (RRR) and 95% confidence intervals and $p < 0.05$ was set for statistical significance. Indicators were created for missing values and all observations were included in the regression analysis. All data analyses were performed using STATA version 13 (StataCorp LP, College Station, Texas, USA).

RESULTS:

The analysis included 17302 nulliparous women who had their mothers' pregnancy records available in the AMND database. The dataset was complete for most of the variables except BMI and smoking status which had 17% and 23% missing values respectively. The characteristics of the study population are shown on Table 1. The median (IQR) age was 23 years (19, 27) and BMI was 23.1 (21.2, 25.8). Almost 40% of the women smoked, of whom majority smoked more than ten cigarettes per day. Of all included women, 1057 (6.1%) had preeclampsia while 4098 (23.7%) gestational hypertension. Four hundred and twenty four (2.5%) were born of pregnancies complicated by preeclampsia while 2940 (17.0%) were born when their mothers had gestational hypertension. The proportion of women born of pregnancies complicated by preeclampsia was higher among those who developed preeclampsia compared to those who developed gestational hypertension or were normotensive (Table 2). Among those who had gestational hypertension, the proportion of women born when their mothers had gestational hypertension was similar to those whose mothers were preeclamptic but higher than among normotensive women (Table 2).

Table 1: Characteristics of Study Participants

Characteristics	All women (n=17302)	Normotensive (n=12147)	Gestational hypertension (n=4098)	Preeclampsia (n=1057)
	N (%)	N (%)	N (%)	N (%)
Age at first pregnancy (median, IQR)	23 (19,27)	22 (19,27)	23 (20,26)	23 (20,26)
Booking body mass index (median, IQR)	23.1 (21.2, 25.8)	22.8 (20.9, 25.3)	23.9 (21.8,27.0)	24.4 (22.2, 27.8)
Social class				
Professional/Non-manual	3438 (19.9)	2358 (19.4)	861 (21.0)	219 (20.7)
Manual	7574 (43.8)	5390 (44.4)	1733 (42.3)	451 (42.6)
Other	6290 (36.4)	4399 (36.2)	1504 (36.7)	387 (36.6)
Smoking status				
Non-smoker	6549 (37.9)	4656 (38.3)	1471 (35.9)	422 (39.9)
1-9 per day	1491 (8.6)	1168 (9.62)	268 (6.5)	55 (5.2)
Over 10 per day	5226 (30.2)	3900 (32.11)	1100 (26.8)	226 (21.4)
Missing	4036 (23.3)	2423 (20.0)	1259 (30.7)	354 (33.5)
Maternal pregnancy induced hypertension				
Neither	13935 (80.5)	9980 (82.2)	3168 (77.3)	787 (74.5)

Maternal gestational Hypertension	2940 (17.0)	1904 (15.7)	818 (20.0)	218 (20.6)
Maternal Preeclampsia	427 (2.5)	263 (2.2)	112 (2.7)	52 (4.9)

The multinomial logistic regression analysis (Table 2) showed that women who were born of pregnancies complicated by preeclampsia were more likely to develop preeclampsia compared to women who were born of normotensive pregnancies (RRR 2.55 95% CI 1.87–3.47). Likewise, women whose mothers had gestational hypertension also had an increased risk of having preeclampsia but the association was not as strong (RRR 1.44 95% CI 1.23–1.69). On the other hand, the risk of having gestational hypertension was similar in those who were born of pregnancies complicated by preeclampsia (RRR 1.37 95% CI 1.09–1.71) and those whose mothers had gestational hypertension (RRR 1.36 95% CI 1.24–1.49). In order to assess the potential effect of missing values on the results, a complete case analysis was also conducted. The model with complete cases included 11506 women but results were similar to that which used indicators for missing values.

Table 2: Association of preeclampsia and gestational hypertension with maternal history of pregnancy induced hypertension

Characteristics	Normotensive (n=12147)	Gestational hypertension (n=4098)				Preeclampsia (n=1057)			
		Unadjusted		Adjusted		Unadjusted		Adjusted	
		RRR (95% CI)	P-value	^a RRR (95% CI)	P-value	RRR (95% CI)	P-value	^a RRR (95% CI)	P-value
Age at first pregnancy (median, IQR)	Reference group	1.01 (1.002–1.02)	0.01	1.01 (1.0004–1.02)	0.04	1.003 (0.99–1.02)	0.67	0.999 (0.98–1.01)	0.46
Booking body mass index (median, IQR)	Reference group	1.0001 (1.00001–1.0002)	0.02	1.00 (0.9999–1.0001)	0.56	1.0002 (1.00007–1.0004)	0.01	1.0002 (1.00006–1.0003)	0.04
Social class Professional/Non-manual	Reference group			1				1	

Manual		0.88 (0.80–0.97)	0.01	0.93 (0.85–1.03)	0.18	0.90 (0.76–1.07)	0.23	0.97 (0.82–1.16)	0.76
Other		0.94 (0.85–1.03)	0.19	0.99 (0.89–1.10)	0.88	0.95 (0.80–1.13)	0.54	1.03 (0.85–1.24)	0.78
Smoking status									
	Reference group	1		1				1	
Non-smoker									
1-9 per day		0.73 (0.63–0.84)	<0.0001	0.75 (0.65–0.87)	<0.0001	0.52 (0.39–0.69)	<0.0001	0.50 (0.37–0.67)	<0.0001
Over 10 per day		0.89 (0.82–0.98)	0.01	0.93 (0.85–1.03)	0.16	0.64 (0.54–0.76)	<0.0001	0.62 (0.52–0.74)	<0.0001
Missing				-	-	-	-	-	-
Maternal pregnancy induced hypertension									
	Reference group			1				1	
None									
Maternal gestational hypertension		1.35 (1.24–1.48)	<0.0001	1.36 (1.24–1.49)	<0.0001	1.45 (1.24–1.70)	<0.0001	1.44 (1.23–1.69)	<0.0001
Maternal Preeclampsia		1.34 (1.07–1.68)	0.01	1.37 (1.09–1.71)	0.01	2.51 (1.85–3.41)	<0.0001	2.55 (1.87–3.47)	<0.0001

^aMultinomial logistic regression analysis was used to assess the association of a woman being born a pregnancy complicated by gestational hypertension or preeclampsia and having either of the conditions themselves in their first pregnancies. The analysis was adjusted for age at first birth, BMI, smoking status and social class.

DISCUSSION:

This study, using intergenerational data from a geographically defined population, suggests that the inherited risk of preeclampsia was different in women born of pregnancies complicated by preeclampsia and those born of pregnancies complicated with gestational hypertension compared to women born of normotensive pregnancies. Women born of pregnancies complicated with preeclampsia had more than twice the risk of developing preeclampsia themselves in their first pregnancies. The risk in those born of pregnancies complicated by gestational hypertension is lower but still higher than those born of normotensive pregnancies. In other words, the inheritance pattern of preeclampsia showed a dose response effect with the highest risk in women born of preeclamptic pregnancies. On the other hand, the risk of having gestational hypertension is very similar in women born of pregnancies complicated by gestational hypertension and those born of pregnancies complicated by preeclampsia.

Our findings are consistent with most other studies that have looked at inherited predisposition to preeclampsia. Previous evidence suggest that women who were born after a preeclamptic pregnancy were more than twice as likely to develop preeclampsia themselves even though other risk factors were not adjusted for (OR 2.2 95% CI 2.0–2.4) [12]. The study also showed that women who were not born to a pregnancy complicated by preeclampsia but had a family history were still at risk of preeclampsia compared with women with no family history of preeclampsia at all. These demonstrate that there are various genetic contributions to the risk. Cnattingius suggested that more than 67% of the susceptibility to preeclampsia is accountable to genetic factors, while 32% to unmeasured “other” factors [14]. However, preeclampsia is a complex disorder with varying grades of clinical severity and so familial risk for preeclampsia is expected to involve combination of genes rather than a single gene [20,21]. A recent meta-analysis of genes which are currently under investigation for preeclampsia showed that over a third of the genes examined were not found to be consistently or significantly associated with preeclampsia [22]. Further work

likely involving genome wide association studies is needed to understand the genetics of preeclampsia.

This study also showed that while those who had preeclampsia were more than twice as likely to have been born of a preeclamptic pregnancy compared to being born of a normotensive pregnancy, for those who had gestational hypertension, the association was not as strong. In fact, the risk of developing gestational hypertension is almost the same for those who were born of preeclamptic pregnancies and those born of pregnancies complicated by gestational hypertension. Comparable observations have been reported by other authors. For example, women who had severe or early onset preeclampsia were more likely to have been born of a preeclamptic pregnancy compared to those born of normotensive pregnancies (OR 3.0 95% CI 2.4–3.7) [12]. However, the association was less in women who had mild preeclampsia (OR 2.1 95% CI 1.8–2.4). These suggest that inherited susceptibility to preeclampsia may cause a more severe disease.

Only nulliparous women were included in this study, some of the women would have had preeclampsia in subsequent pregnancies. However, preeclampsia is predominantly a condition occurring in the first pregnancy, its presence in a subsequent pregnancy is often preceded by a history of the condition in the initial pregnancy [23]. Multiparous women with no history of preeclampsia only had about 1% risk of preeclampsia but those that had preeclampsia in one or two consecutive pregnancies had much higher risks, about 15% and 30% respectively [24]. More so, a study which investigated the familial risk of preeclampsia in the second birth showed that women born of pregnancies complicated by preeclampsia still had similar risk (OR 2.3 95% CI 1.8–2.9) [12]. We have no reasons to believe that the risks would be significantly different in the subsequent pregnancies.

One of the strengths of this study is that the diagnoses were made based on established criteria. Also, AMND data are coded contemporaneously as the events occur and thereby

eliminate recall bias. Recently data have become available in the Scandinavian countries from their birth registries by means of which the genetic component of preeclampsia can be tested. Although these are extremely large population based cohorts, they lack data on other important risk factors such as smoking. It is worth noting that smoking habits in the dataset used for this study were recorded based on self-report. Self-reported information on habits which are deemed socially undesirable, such as smoking during pregnancy, are often inadequate. Some women may underreport that they smoked or the number of cigarettes they smoked daily. Yet, in the cohort used in this study, the proportion of smokers is as high as 39%. Although this is partly due to the historic cohort, the proportion of smokers among women who delivered between year 2000 and 2007 was still about 29%. It is unlikely that smoking was significantly underreported in this study. More so, the inverse relationship observed with smoking in this study is consistent with what has been reported in several previous studies [4].

While we adjusted for potential confounding factors, there were some known (such as, past medical history of hypertension and/ or renal disease) and other unknown factors that could not be taken into consideration which is a limitation of our study. Nevertheless, factors such as history of hypertension could be a path variable and it would not be necessary to adjust for it in this study. We also did not assess the daughters' risk of preeclampsia or gestational hypertension if their mothers were hypertensive in another pregnancy resulting in a sibling's birth. We acknowledge that although not as strong as maternal associations, predisposition to preeclampsia may also be inherited from fathers as shown in other epidemiological studies [25]. We did not assess associations with paternal history of preeclampsia as it is beyond the scope of this study.

In conclusion, this study showed that women born while their mothers had preeclampsia were more than twice as likely to develop preeclampsia compared to those born of normotensive pregnancies even after adjusting for other factors. Maternal history of

gestational hypertension also contributes to the risk of preeclampsia, albeit not as much as maternal history of preeclampsia. Inherited predisposition to preeclampsia is more pronounced for clinically more severe disease. Further studies are required to enable the clinician to accurately predict the development of preeclampsia at the antenatal visit and plan the management of pregnancies accordingly. Such studies may include prospectively collected information such as uterine artery Doppler, fetal DNA in maternal circulation and other biochemical tests that have been demonstrated to predict preeclampsia.

Competing Interests: All authors declare that they have no competing interests

Contribution to authorship: SB conceived of the research idea while AA conducted the analysis. Both authors were involved in interpretation of data, drafting and critically appraising the manuscript and also approved the final version to be submitted.

Ethical approval: The North of Scotland Research Ethics Committee declared that formal ethical approval was not required for this research as only routinely collected anonymised data were being analysed.

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Highlights

- We identified a dose response effect in the inheritance pattern of preeclampsia.
- Maternal gestational hypertension was associated with increased risk of preeclampsia in daughters.
- The risk of preeclampsia was higher in women born from preeclamptic pregnancies.
- Inherited susceptibility to preeclampsia is associated with severity of the condition.

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